Rational Use of Benzodiazepines

Benzodiazepines are used in medicine primarily for anxiety disorders, insomnia, acute treatment of agitation, and treatment of substance abuse withdrawal syndromes. Less frequent uses in other disorders are discussed in the body of this monograph. While there are clear benefits from this class of medications, inappropriate use can result in significant disadvantages for patients. Researchers cite adverse effects after long-term use and the potential for misuse and abuse by patients at risk for or having addiction. Research has helped us to understand the role of these medications and it is the goal of this communication to provide a guide to using benzodiazepines effectively in treating anxiety disorders and insomnia.

Anxiety disorders and insomnia are the most common psychiatric disorders for which benzodiazepines are used

Anxiety disorders

Benzodiazepines are potent anxiolytic agents and are effective both in healthy patients undergoing severe stress and in patients suffering from anxiety. The major clinical advantage of benzodiazepines as anxiolytics is the rapid onset of action, usually apparent after a single dose. This immediate effect contrasts with the delayed anxiolytic effects of antidepressants, buspirone, and psychological treatments. The efficacy for antidepressants and psychological treatments, such as cognitive behavioral therapy (CBT), are well established as effective for treatment of panic disorder and are considered the first line of treatment by experts. The evidence is not yet clear on the efficacy advantages of one modality over the other for patients with generalized anxiety disorder (GAD) and generalized social phobia. In the case of patients with acute stress disorder (ASD), post traumatic stress disorder (PTSD) or specific phobias, evidence points to psychotherapy as the treatment of choice. The choice between psychotherapy and pharmacotherapy depends on an individualized assessment of the efficacy, benefits and risks of each modality, as well as the patient's personal preferences (including costs).

Reasons to use benzodiazepines for treatment of anxiety:

- Benzodiazepines are preferred in situations in which very rapid control of symptoms is critical (e.g., the patient is about to quit school, lose a job or require hospitalization).
- Concomitant benzodiazepine use may be helpful to provide immediate symptom relief until CBT or pharmacotherapy becomes effective, or for some patients with severe panic attacks or high levels of anticipatory anxiety.

Reasons to <u>avoid</u> long-term use of benzodiazepines:

- Long-term benzodiazepine use is associated with tolerance, although physicians report some cases of patients who do not develop tolerance. Benzodiazepines

must be used cautiously in patients with a history of substance use disorder, given their vulnerability to addiction.

- Many patients with anxiety disorders also suffer from depression. Benzodiazepines are ineffective for depression and may aggravate it. Antidepressants are effective for both illnesses in patients suffering from co-morbid anxiety and depression.
- Benzodiazepines increase the risks of traffic and other accidents (especially when combined with alcohol) by impairing psychomotor performance.
- Benzodiazepines are potential drugs of abuse.
- Iatrogenic benzodiazepine dependence is possible.
- Long-term use is associated with cognitive deficits, especially in visuospatial and learning ability.
- Benzodiazepines increase the risks of falls and fall related injuries, especially in the elderly.

Guideline for Use of Benzodiazepines in Treatment of Anxiety

Anxiety state	Duration of treatment	Other treatment
Situational Reactions	Benzodiazepines not recommended	Psychological treatment
Phobia prophylaxis (e.g., dental appointments, air travel	Single dose before event	Psychological treatment
Bereavement	Single doses for a few days, only if distress is severe	Psychological treatment
Adjustment Disorders	Single doses or a few days only initially—not suitable for long term management	Psychological treatment, Antidepressants
ASD/ Post Traumatic Stress Disorder	Single or intermittent courses (2-4 weeks followed by 1-2 weeks in tapering doses) Use in conjunction with other treatments	Psychological treatment is first-line, Antidepressants
Episodic Anxiety Chronic Generalized Anxiety	Single or intermittent courses (2-4 weeks followed by 1-2 weeks in tapering doses) Use in conjunction with other treatments	Antidepressants, ß-blockers, Psychological treatment
Panic Disorder	Initial course 2-4 weeks (if symptoms severe) while a first line treatment of behavioral therapy or antidepressants is initiated	Antidepressants, Psychological treatment
Social Phobias		Antidepressants, Psychological treatment
Obsessive Compulsive Disorder		

Longer-term benzodiazepine treatment, used on a regular schedule, may be considered in the management of persistent anxiety disorders in the following two cases:

- Adjunct for patients partially responsive to other treatments; and
- Alternative to antidepressants when these are not tolerated.

Insomnia

Insomnia is a prevalent condition affecting many age groups. Insomnia itself is not a disorder, but rather a symptom that has many etiologies. Etiologies can be broadly classified as physical (pain, medical illness), physiological (jet lag, shift work), psychological (worry), pharmacological (caffeine, stimulant medications), and psychiatric (depression).

The first and most important step in the treatment of insomnia is to understand the etiology. In many cases, treatment of the underlying etiology, such as depression, results in improvement of sleep pattern. Readjustment of the sleep schedule or introduction of other non-pharmacologic strategies often aids the sleep pattern. Sleep inducing medications may be used when the above is not indicated and/or does not work. These should be used for brief periods, as indicated below, and tapered if necessary to reduce the risks of tolerance or addiction. Benzodiazepines should be generally avoided in favor of the newer non-benzodiazepines (zolpidem [Ambien] or zaleplon [Sonata]).

Transient insomnia secondary to disruption of normal sleep cycle from such things as change in time zone, admission to a hospital, or change in shift work can be treated with short acting non-benzodiazepines (zolpidem, zaleplon) and other non-pharmacologic insomnia treatments, but not for more than three to four total treatments.

For **Short-term insomnia** resulting from temporary environmental stress, short-acting benzodiazepines, newer non-benzodiazepines (zolpidem [Ambien], zaleplon [Sonata] and other insomnia treatments can be useful on a short-term basis (1 – 2 weeks) or intermittently.

Chronic insomnia is usually due to secondary conditions (medical or psychiatric). Every effort should be made to address these conditions. If hypnotics are still required, they should be used at the lowest dose possible, intermittently or in short courses.

Do not forget that **good sleep starts with good sleep hygiene**. Encourage your patients to follow these guidelines:

1. Keep a consistent pattern of waking and sleeping at the same time each day.
2. Avoid large meals before bedtime.
3. Limit caffeine, alcohol, or nicotine use.
4. Avoid daytime naps.
5. Engage in regular exercise, but avoid exercise just before sleeping.
6. Allow for a period of relaxation before bedtime.
7. Avoid using the bed for reading, watching television, talking on the telephone or eating, activities not associated with sleep.
8. If one does not fall asleep after 20 minutes in bed, get up and sit in a chair, do something relaxing until feeling tired and return to bed.

Please Note: Some practitioners prescribe atypical antipsychotic medications, to treat insomnia. These drugs are associated with clinical risks and high costs and are not advised in the treatment of insomnia.

1. Benzodiazepines alter the normal sleep pattern.
2. Tolerance can develop rapidly.
3. Hangover effects are common with longer acting benzodiazepines.
4. Rebound insomnia can occur when benzodiazepines are discontinued after extended use; these may cause falls and cognitive impairment.
5. Dependence can develop after several weeks of use, repressing risk for patients prone to addiction.
6. Respiratory depression can impact patients with severe COPD, so consult with the COPD patient's pulmonologist to determine whether unrelated anxiety or potential respiratory depression will put a greater demand on the system of the COPD patient.

Guideline for Use of Benzodiazepines in Treatment of Insomnia

Type of insomnia	Dosage Guidelines
Transient insomnia (e.g., disruption of circadian rhythm)	1-2 nights only, minimal dosage
Short term insomnia (e.g., temporary environmental stress)	Not for more than 2 weeks. Intermittent if possible (1 night in 2 or 3 nights). Minimal effective dosage (start with small dose; increase if needed)
Chronic insomnia (e.g., secondary to physical, psychological or psychiatric causes)	Treat primary cause first. Intermittent treatment if possible. Not more than 2 weeks (course may be repeated after an interval). Minimal effective dosage

Benzodiazepine and newer non-benzodiazepines (zolpidem [Ambien], zaleplon [Sonata] used for the treatment of insomnia

Source: Clinical handbook of Psychotropic Drugs, 13th Ed 2003

Agent	Dosage	Half-life of Metabolites (Range)	Comments
flurazepam (Dalmane)	15-30 mg qhs	40.0 - 250.0 hours	Hangover is common. Can accumulate in elderly. **AVOID**
temazepam (Restoril)	7.5-30 mg qhs	3.0 - 25.0 hours	Intermediate acting, half-life is well-suited to its role as a hypnotic: 6-8 hours in most patients
triazolam (Halcion)	0.125-0.25 mg qhs	1.5 – 5.0 hours	Short acting; some patients can experience perceptual disturbances
zaleplon (Sonata)	5 -10 mg	0.9 – 1.1 hours	Non-benzodiazepine; no daytime hangover

zolpidem (Ambien)	5-10 mg qhs	1.5 - 4.5 hours	Non-benzodiazepine; no daytime hangover

How can benzodiazepines be discontinued when they have been used chronically?

One method for discontinuing longer acting benzodiazepines is to convert patients to an equivalent dose of clonazepam (Klonapin), chlordiazepoxide (Librium) or diazepam (Valium) (Zitman), although this is not universally accepted. Many patients do poorly with a switch from alprazolam to diazepam. Diazepam has a very long half-life; clonazepam and chlordiazepoxide have longer half-lives which reduce the likelihood of withdrawal symptoms.

Guideline for Dosage Equivalencies

Reference: Kaplan and Sadock 1995.

Benzodiazepine	Equivalent
1 mg of clonazepam (Klonapin)	20 mg of diazepam (Valium)
10 mg of diazepam (Valium)	1 mg alprazolam (Xanax)
10 mg of diazepam (Valium)	20 mg chlordiazepoxide (Librium)
10 mg of diazepam (Valium)	15 mg clorazepate (Tranxene)
10 mg of diazepam (Valium)	30 mg flurazepam (Dalmane)
10 mg of diazepam (Valium)	2 mg lorazepam (Ativan)
10 mg of diazepam (Valium)	20 mg temazepam (Restoril)
10 mg of diazepam (Valium)	30 mg oxazepam (Serax)

Please Note: These equivalents are approximate and do not reflect the consensus in all texts

1. Daily dose can be reduced by 25% in both the first and second week.
2. The remaining 50% can be tapered off in four steps of 12.5% each in weeks three and four.
3. In patients who have been treated long-term with benzodiazepines for a major anxiety disorder, tapering should be slower to prevent re-emergence of symptoms.

A second option for discontinuing short-acting benzodiazepines is:

1. Dose frequently on a standing schedule during taper (e.g. minimum four times daily for alprazolam (Xanax), three times daily for lorazepam (Ativan) and chlorazepate (Tranxene)).
2. Systematically reduce each dose.
3. When down to lowest available dose, then decrease frequency.

There is little evidence for the effectiveness of long-term benzodiazepines in the following psychiatric disorders: schizophrenia, schizoaffective disorder, bi-polar illness and depression.

Bipolar Disorder

Benzodiazepines have been studied in randomized controlled trials for treatment of acute bipolar mania. Among the benzodiazepines, clonazepam (Klonopin) and lorazepam (Ativan) have been studied alone and in combination with lithium. Because of small study group sizes, short treatment durations, concomitant antipsychotic use, and difficulties in distinguishing antimanic effects from nonspecific sedative effects, the studies are of limited usefulness. Taken together, however, these studies suggest that the sedative effects of benzodiazepines may make them effective treatment adjuncts while awaiting the effects of a primary antimanic agent to become evident. The fact that lorazepam, unlike other benzodiazepines, is well absorbed after intramuscular injection has made it particularly useful for the management of agitation. However, intramuscular antipsychotics are superior to intramuscular lorazepam in ameliorating agitation in patients with bipolar mania (Meehan, 2001).

Schizophrenia

Double-blind studies evaluating benzodiazepines as adjuncts to antipsychotic medications were reviewed by Wolkowitz and Pickar (1991). Only seven of 16 studies showed some positive effect on anxiety, agitation, psychosis, or global impairment; five of 13 showed efficacy in treating psychotic symptoms specifically. Where there was efficacy, it tended to be limited to the acute phase and not sustained. A more consistent finding was efficacy for patients with prominent agitation. The reviewers concluded that benzodiazepines as adjuncts to antipsychotic medications are most likely useful in the acute management of psychotic agitation.

Other Uses

They are less frequently used as adjunctive treatment for certain symptoms of several other disorders; these include seizure disorders, movement disorders, muscle spasms and management of medication side effects.

References

American Psychiatric Association. (1997). Practice guideline for the treatment of patients with schizophrenia. *American Psychiatric Press*.

American Psychiatric Association. (1998). Practice guideline for the treatment of patients with panic disorder. *American Psychiatric Press*.

American Psychiatric Association. (2002). Practice guideline for the treatment of patients with bipolar disorder. *American Psychiatric Press*.

Ashton, H. C. (1994). Guidelines for the rational use of benzodiazepines: When and what to use. *Drugs, 48*(1), 25-40.

Ballas, C., Staab, J. P, & Evans, D. L. (2002). *Psychopharmacology Bulletin* (Supplement 3): 39-62.

Bazire, S. (1994). *Psychotropic drug directory*. Salisbury: Mark Allen Publishing.

Bezchilbnyk-Butler, K. Z., & Jeffries, J. J. (Eds.). (2003). *Clinical handbook of psychotropic drugs* (13th ed.). Toronto, Canada: Hogref & Huber Publishers.

Cochran, H. (2003). Diagnose and treat primary insomnia. *Nurse Practitioner*, 28:9, 13-27.

Hahn, R. K., Albers, L., & Reist, C. (Eds.). (2003). *Psychiatry* (2003-2004 ed.). Current Clinical Strategies Publishing.

Kaplan, H., & Sadock, B. (Eds.). (1995). *Comprehensive textbook of psychiatry* (6th ed.). Baltimore, MD: Williams and Wilkins Publishing.

Meehan, K., Zhang, F., David, S., & Tohen, M., et al. (2001). A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *Journal of Clinical Psychopharmacology, 21*, 389-397.

Schenck, C.H, Mahowald, M.W., Sack, R.L. (2003). Assessment and Management of Insomnia. *JAMA*, 289:19, 2475-2479.

Wolkowitz, O.M., & Pickar, D. (1991). Benzodiazepines in the treatment of schizophrenia: A review and reappraisal. *American Journal of Psychiatry,* 148, 714-726.

Zitman, F. G., & Couvee, J. E. (2001). Chronic benzodiazepine use in general practice patients with depression: An evaluation of controlled treatment and taper-off (report on behalf of the Dutch Chronic Benzodiazepine Working Group). *British Journal of Psychiatry, 178*, 317-324.